Data and Safety Monitoring Boards: Interim Monitoring for Clinical Trials

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DSMB is responsible for monitoring the trial

Data and Safety Monitoring Board (DSMB)

Primary charge: Oversee patient (participant) safety

particular issue in masked trials but even for unmasked trials investigators not informed as to overall results

DSMB - Description

- **Generally 3 – 10 members**
- **Members reflect disciplines needed to evaluate the trial**
  - **clinical**
  - **biostatistics**
  - **ethics**
  - **patient advocate (more recent/disease)**
- **No member associated with trial in any other capacity**
- **Appointed by sponsors of trial**
- **Ex-officio members**
  NIH (if applicable
  Industry sponsor (yes or no?)
  Trial Statistician
  Principal Investigator(s) (yes or no, masked?)

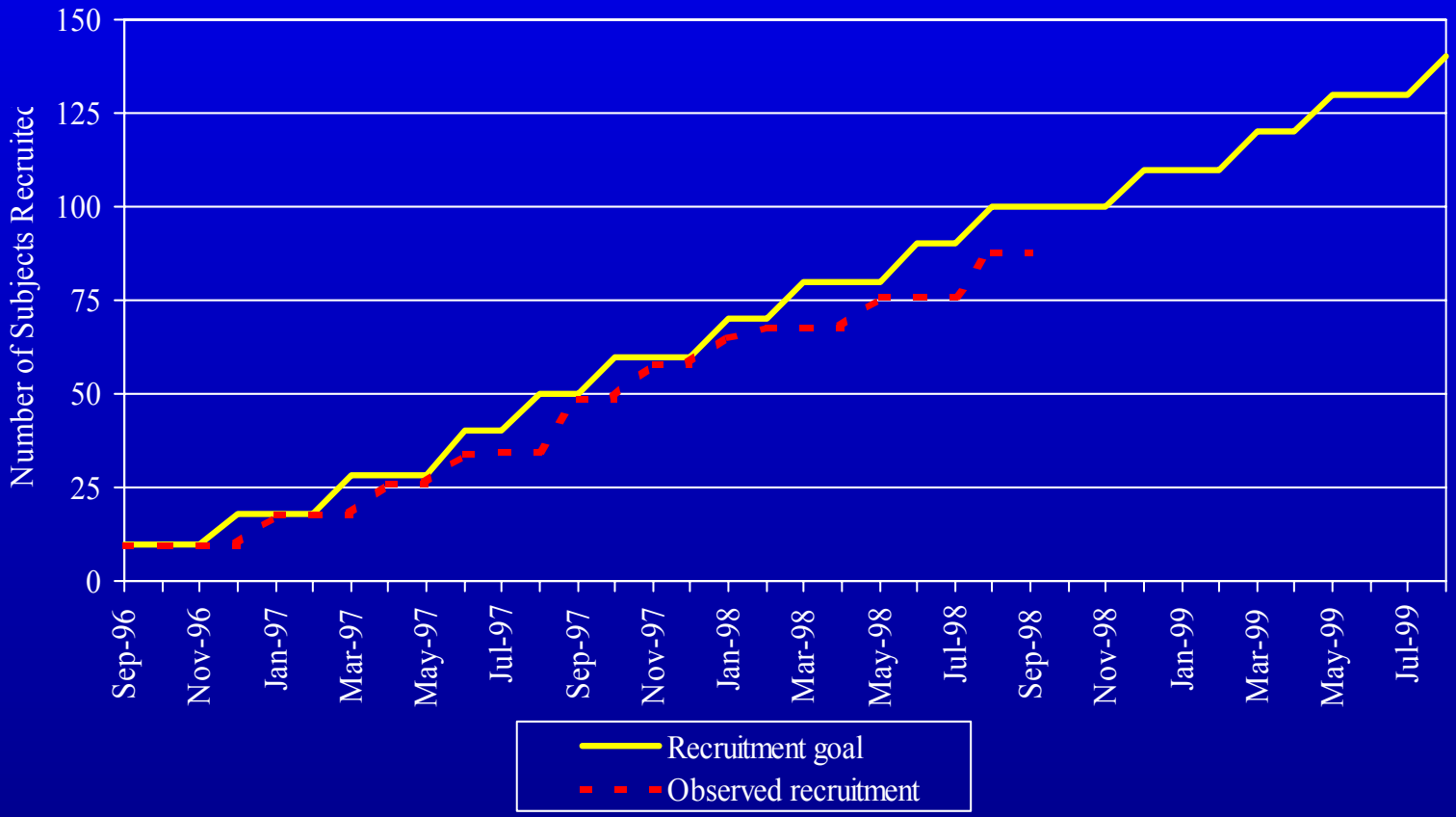
DSMB's Responsibilities

- Address ethical issues
- Review protocol before initiation of trial
- Review interim reports
  - recruitment
  - compliance
  - adverse effects
  - baseline comparability
  - treatment comparisons
- Meet often enough to carry out responsibilities – in general once per year
  - additional meetings or conference calls if needed
- Each meeting make recommendation that trial should stop, continue or continue w/modifications

Recruitment Reports

- Is the study or are the sites recruiting as many subjects as expected?
- If not, may recommend….
  - Remove sites
  - Add sites
  - Extend recruitment
  - Terminate trial

Cumulative Recruitment by Month
As of September 28, 1998



Coordinating Center, University of Pittsburgh, Epidemiology Data Coordinating Center,
127 Parran Hall, 130 DeSoto Street, Pittsburgh, PA 15261, Telephone: 412/624-5447, FAX: 412/624-3775

Compliance

Assessment of compliance of…

- treatments
- inclusion of ineligible subjects
- dropouts
- completion of appropriate data collection forms
- certified assessors completing assessments
- proper treatment assignments

Adverse Effects

- Dependent on type of study
  - death
  - additional procedures
  - additional episodes or events
  - hospitalization
  - side effects (e.g. depression, nervousness, muscle aches)
- By site (if multi-site)
- By treatment group
- For drug trials very specific FDA regulations

Baseline Comparisons

Compare baseline characteristics of population by treatment assignment to: profile patient population

check balance

Treatment Comparisons

- Compare the treatments the trial to see if there are any differences
- Problem: If each comparison has a Type I error rate of .05, the chances of finding a false significant difference increase (classical statistical theory)

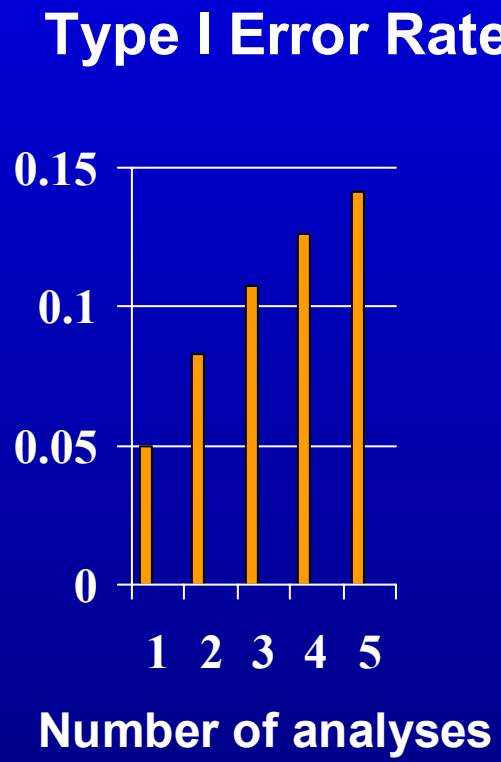
Example
2.5 years recruitment
One year follow-up

Treatment comparisons will be conducted every six months

- 1st analysis: 20 % of subjects complete year 1 visit
- 2nd analysis: 40% of subjects complete year 1 visit
- 3rd analysis: 60% of subjects complete year 1 visit
- 4th analysis: 80% of subjects complete year 1 visit
- 5th analysis: 100% of subjects complete year 1 visit

Example

- Total of 5 analyses
- If the Type I error rate at each of the analyses is .05, then the true Type I error rate is...



- **Several methods for adjusting the Type I error rate**

- **Using these methods the Type I error rate is adjusted at each of the interim analyses so an overall Type I error rate of .05 can be maintained.**

Pocock

- **Reference:**
  Pocock SJ. Group sequential methods in the design and analysis of clinical trials. Biometrika, 1977; 64:191-199.

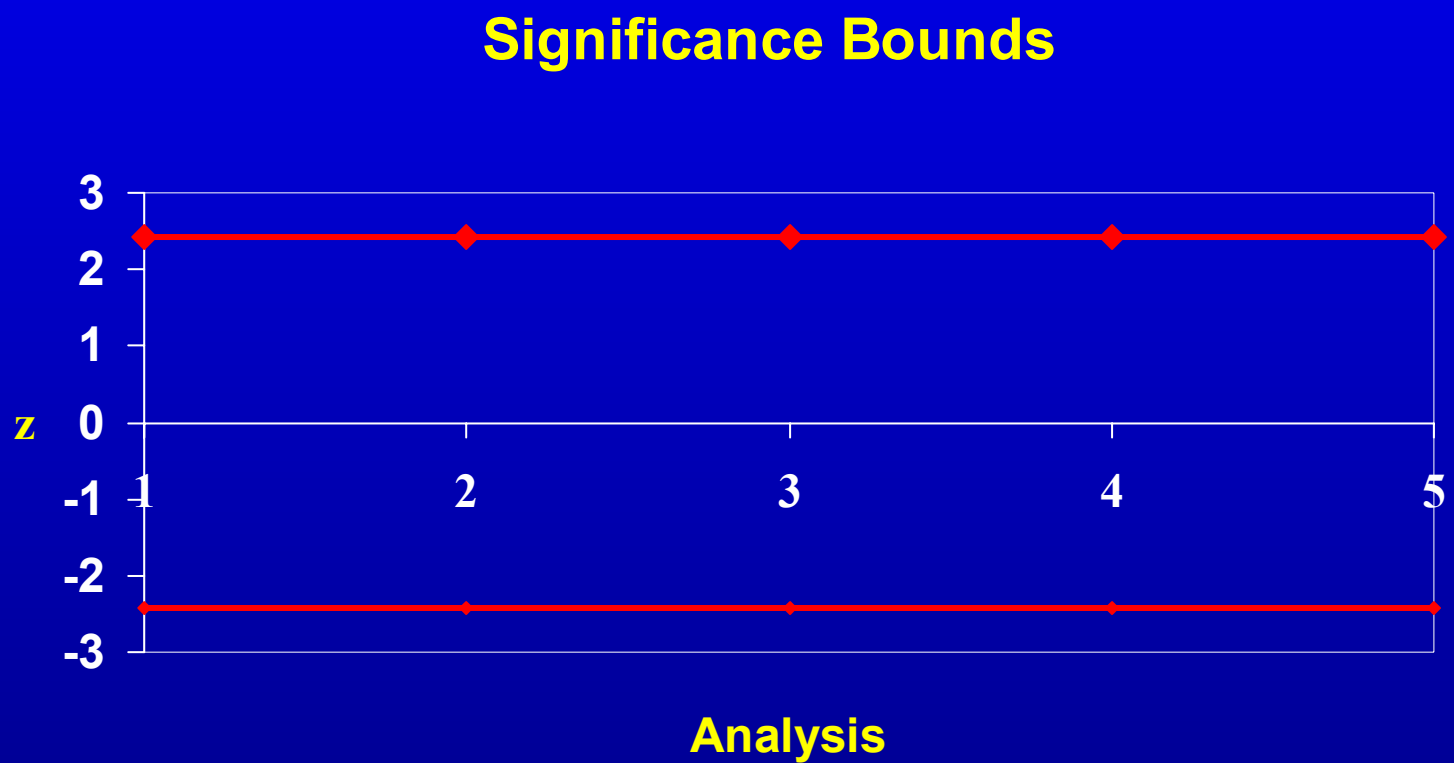
- **Basic concept: keep the adjusted Type I error rate at each of the interim analyses the same (but less than .05) to maintain the overall Type I error rate of .05.**

Pocock

	Number of Looks			
	2	3	4	5
Adjusted Type I error rate	.0294	.0221	.0182	.0152
Z	2.178	2.281	2.361	2.413

For a normally distributed outcome. Where Z=Value from standard normal distribution corresponding to adjusted Type I error rate

Pocock



For 5 analyses

Pocock

- Problem: With constant adjusted Type I error rate, we don't have much Type I error left for the final comparison.

- Solution: "Spend" little of the Type I error at the earlier analyses, saving the majority for the final analysis.

O'Brien & Fleming

- **Reference:**
  O'Brien PC and Fleming TR. A Multiple Testing Procedure for Clinical Trials. Biometrics, 1979; 35:549-556.

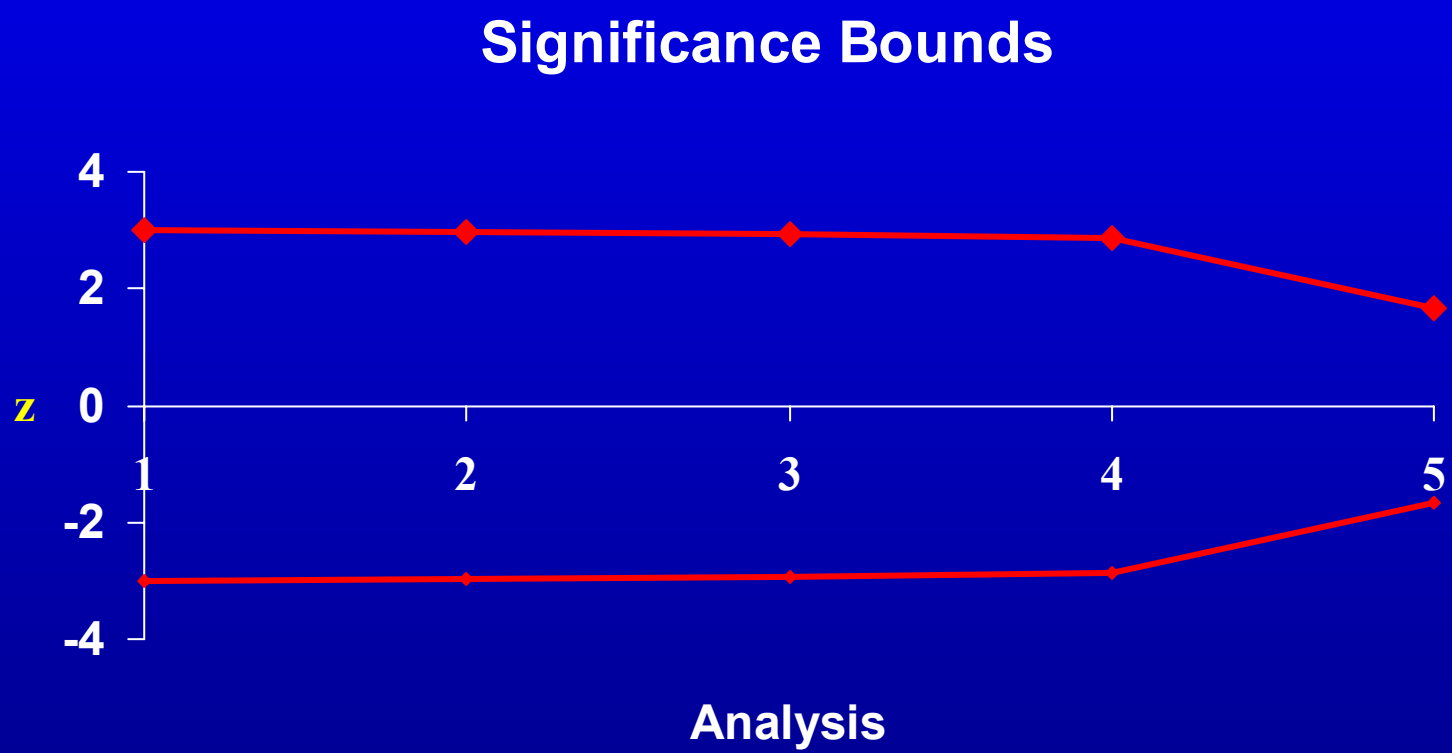
- **Basic concept: Keep the adjusted Type I error rate small early on, increasing the adjusted Type I error rate over time, maintaining the overall Type I error rate.**

O'Brien & Fleming example

	Look Number				
	1	2	3	4	5
Adjusted Type I error rate	.00128	.00144	.00164	.00219	.04806
Z	3.00	2.98	2.94	2.85	1.67

Where:
5 planned looks
Z=Value from Standard Normal distribution corresponding to adjusted Type I error rate

O’Brien & Fleming



For 5 analyses (looks)

O'Brien & Fleming

- Problem: What if recruitment is slower than expected, or the Safety and Data Monitoring Board Requests more analyses. The two methods presented thus far are designed for planned interim analyses.

- Solution: A spending function that does not depend on the total number of analyses.

Lan & DeMets

- **Reference**

  Lan KKG and DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika, 1983;70:659-663.

- Basic concept: The Type 1 error is spent on a function that is dependent on past and current analysis times, not future times or the total number of analyses.

- "Spending the alpha"

Other Monitoring Tools

Bayesian Methods

- Assessment of evidence does not depend on plan for future analysis (no "alpha spending")

Conditional Power

- What is the probability that a difference will be detected at the end given the data so far.

DSMB Decision Making Process

- Decision to stop a trial not purely statistical
- Magnitude of difference must be considered
- Possible subgroup effects
- Should the protocol be modified?

Some Reasons Why a Clinical Trial Might be Stopped Early

- Treatments are found to be convincingly different by impartial knowledgeable experts.
- Treatments are found to be convincingly not different by impartial knowledgeable experts.
- Side effects or toxicity are too severe to continue treatment in light of potential benefits.
- The data are poor quality
- Accrual is too slow to complete the study in a timely fashion.
- Definitive information becomes available from outside the study, making the trial unnecessary or unethical.
- The scientific question are no longer important because of other developments.
- Adherence to the treatment is unacceptably poor, preventing an answer to the basic question.
- Resources to perform the study are lost or no longer available.
- The study integrity has been undermined by fraud or misconduct.

Disadvantages of Stopping Early

- **Lack of credibility**
  - **small trials not convincing**
- **Bias/Mistake**
  - **Trial liable to stop on "random high", risk of false positive**
- **Pressure**
  - **unduly enthusiastic and extrapolated recommendation may follow**
- **Long term outcome not well known**

Confidentiality of Interim Reports

May change investigators outlook and participation based on results that are not complete

- Should industry sponsors/supporters have access?

Turn in reports at the end of the meeting

- **Though DSMB members are very interested in the science and can make valuable suggestions for the design execution and analysis of a trial, must keep in mind that patient safety is primary focus to ensure an ethical trial**